PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ZR-1154-1217	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IN2004/000341	International filing date *(day/month/year)* 02.11.2004	Priority date *(day/month/year)* 03.11.2003
International Patent Classification (IPC) or national classification and IPC C07D495/04		
Applicant CADILA HEALTHCARE LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 14 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.05.2005	19.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Johnson, C Telephone No. +49 89 2399-8287

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000341

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-19 as originally filed

   Claims, Numbers

   1-24 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1(part),3(part),6(part)10-15(part),22(part)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1(part),3(part), 6(part)10-15(part),22(part) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1(part),3(part),6(part)10-15(part),22(part) are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IN2004/000341

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	23,24
Inventive step (IS)	Yes:	Claims	1-15,20
	No:	Claims	16-19,21,23,24
Industrial applicability (IA)	Yes:	Claims	1-22,24
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

III. Non-establishment of opinion

The subject matter of each claim must be supported by the description in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art over the entire scope (Articles 5 and 6 PCT, Guidelines 5.45, 5.48). This does not appear to be the case with present claim 1: the technical features of this claim are i) the treatment of Clopidogrel base with dilute H_2SO_4 in one or more suitable solvents, followed by ii) removal of the solvent and isolation of the amorphous form by addition of one or more suitable antisolvents. In order for this claim to be clear and sufficiently disclosed, the skilled man must, without undue experimentation, be able to reliably and reproducibly prepare the amorphous hydrate by reproducing these process steps. However, in example 21 of WO03/051362 (cited in the present description) these process steps are reproduced, but the recovered product is a mixture of the crystalline form I and the amorphous form (which, according to the applicant's statement on p. 3, l. 14-15 is different from the amorphous hydrate). A further example in this document, ex. 27, uses the presently claimed process steps but gives the product in its crystalline form III. Yet another variant (ex. 44) using the presently claimed process steps leads to recovery of product in its crystalline form VI. Thus the skilled person would not be able to prepare the desired amorphous hydrate using all processes covered by claim 1. Furthermore, the above-described examples use as the suitable solvent solvents which are listed in present dependent claim 7. Hence, even using the further technical features of claim 7, the skilled man would be unable to reliably and reproducibly prepare the desired amorphous hydrate using all processes covered by claim 1 in combination with claim 7. In view of the lack of compliance of claim 1 with Articles 5 and 6 PCT, this claim cannot be searched or examined in any meaningful way. For this reason, claim 1 has only been searched and examined insofar as the suitable antisolvent is a solvent listed in claim 8. As claims 3 and 6 differ from claim 1 only insofar as they contain the additional step of first preparing the clopidogrel base, but otherwise contain only the same technical features as claim 1 for converting the base into the desired amorphous hydrate salt, these claims also are insufficiently disclosed for the same reasons as given for claim 1. Hence claims 3 and 6 have only been searched and examined insofar as they use one of the antisolvents listed in claim 8.

Claim 10 is also insufficiently disclosed so that a person skilled in the art cannot carry out the invention over its entire scope. The technical features of this claim are i) the treatment of clopidogrel base with dilute H_2SO_4 in one or more suitable solvents and ii) the isolation of crystalline formula I. WO03/051362 discloses dissolution of clopidogrel base in acetone followed by addition of aqueous sulfuric acid (example 17). The product which is isolated from this reaction mixture is the amorphous form, not crystalline form I. Thus claim 10 does not contain all essential technical features necessary to obtain the desired product.

Claim 11 is also insufficiently disclosed so that a person skilled in the art cannot carry out the invention over its entire scope. The technical features of this claim are i) the treatment of clopidogrel base with conc. H_2SO_4 in one or more suitable solvents and water and ii) the isolation of crystalline formula I. WO2004/081016 discloses a process with the same technical features as this claim (example 21) but the product which is isolated from this process is the amorphous form, not crystalline form I. Thus claim 11 does not contain all essential technical features necessary to obtain the desired product.

Claim 12 is also insufficiently disclosed so that a person skilled in the art cannot carry out the invention over its entire scope. The technical features of this claim are i) the dissolution or contacting of clopidogrel bisulfate with one or more suitable solvents and ii) the isolation of crystalline formula I. Example 29 of WO03/051362 discloses the dissolution of clopidogrel bisulfate in isopropanol. The product recovered from this solution is form IV, not the presently claimed form I. Thus claim 12 does not contain all essential technical features necessary to obtain the desired product.

Claim 13 is also insufficiently disclosed so that a person skilled in the art cannot carry out the invention over its entire scope. The technical features of this claim are i) the treatment of clopidogrel bisulfate with one or more suitable solvents and water and ii) the isolation of crystalline formula I. WO2004/081016 discloses a process with the same technical features as this claim (example 15) but the product which is isolated from this process is the amorphous form, not crystalline form I. Thus claim 13 does not contain all essential technical features necessary to obtain the desired product.

Claims 14 and 15 differ from claims 10 and 11 in that the way in which the clopidogrel base is obtained before its conversion to the bisulfate crystalline form I is defined. However, the origin of the base is irrelevant to the outcome of the process of preparing the bisulfate salt. Thus, as already explained above for claims 10 and 11, the technical features of claims 14 and 15 do not include all essential information necessary to obtain the desired crystalline form I, as the skilled person performing processes falling within the scope of these claims could equally well obtain the amorphous form as form I.

Claims 10-15 have therefore only been searched insofar as they appear to be sufficiently disclosed, namely insofar as the suitable solvent used in the processes of these claims is a C_6-C_{12} alcohol as defined in claim 20.

Claim 22 is insufficiently disclosed. The technical features of this claim are i) the stirring of amorphous clopidogrel bisulfate in MTBE and ii) the removal of the solvent to give form II. WO03/051362 discloses an example (ex. 21) in which (S)-(+)-Clopidogrel bisulfate in a non-crystalline form (white foam) is stirred in MTBE and a solid is recovered. This solid is a mixture of amorphous form and form I. Thus, it would appear that essential technical features are missing from this claim, as the claimed process does not reliably and inevitably give the desired form II. As there are no preferred embodiments for this claim (i.e. dependent claims) it is not clear which further feature(s) could be inserted in this claim in order to give a process which reproducibly gives the desired polymorph. It was therefore not possible to perform any meaningful search or examination of this claim. In the applicant's opinion, the amorphous form referred to in claim 22 refers to the amorphous hydrate form of clopidogrel bisulfate prepared according to any of the processes of claims 1-9, and this amorphous hydrate form is unique and distinct from that disclosed in WO03/051632. However, this is not reflected by the wording of claim 22 ("a process for the preparation of form II of (S)-(+)-Clopidogrel bisulfate comprising stirring the different amorphous forms in methyl-tert-butyl ether and subsequent removal of the solvent"). Limitations which are not in the claims cannot be considered when assessing the conformity of the claims with the articles and rules of the PCT.

IV. Lack of unity

The present claims cover the following subject-matter:
Claims 1-9: processes for the preparation of hydrated form of amorphous (S)-(+)-Clopidogrel bisulfate.
Claims 10-21: processes for the preparation of form I of (S)-(+)-Clopidogrel bisulfate.
Claim 22: process for the preparation of form II of (S)-(+)-Clopidogrel bisulfate.
Claim 23: method of treating cardiovascular and related diseases using the various forms of (S)-(+)-Clopidogrel bisulfate prepared according to the present invention.
Claim 24: use of the different forms of (S)-(+)-Clopidogrel bisulfate prepared according to the present invention for the preparation of a medicine.

Where a group of inventions is claimed in one and the same international application, the requirement of unity referred to in Rule 13.1 PCT shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art (Rule 13.2 PCT).

In the present case, the only technical feature shared by all groups of claims is the fact that they all involve the compound (S)-(+)-Clopidogrel bisulfate. However, as this compound is already known (see e.g. WO03/051362, p. 2, l. 19), this cannot form the unifying special technical feature. For this reason, claims 23 and 24 do not appear to be unitary with process claims 1-22 (it should be noted that the fact that claims 23 and 24 use compounds prepared according to the processes of claims 1-22 does not make these claims unitary with the process claims: products are not rendered new simply because of the process by which they are produced, unless that process reliably leads to a product which is distinguishable from the prior art in some way [see PCT Guidelines 5.26 and A5.26[1]]. In the present case at least the products produced by the processes of claims 10-22 are *a priori* not new (see references cited on p. 2 of the present description). Therefore, even if it is stated that these products are prepared according to the processes of the present invention, there is no common novel special technical feature between the process claims and the use claims, and they are hence not unitary with one another).

The technical feature shared by claims 1-21 and claim 22 is the addition of a solvent to Clopidogrel or a salt thereof, followed by removal of the solvent. However, such a process is already known (see e.g. WO03/051362, example 21). Thus this feature cannot form the special technical feature required by Rule 13.2 PCT. Claim 22 is therefore not unitary with claims 1-21.

The technical feature shared by claims 1-21 is the fact that Clopidogrel or a salt thereof is treated with sulfuric acid. However, the treatment of Clopidogrel with sulfuric acid is already known (see e.g. WO03/051362, example 21). Thus this feature cannot form the special technical feature required by Rule 13.2 PCT. Claims 1-9 are thus non-unitary with claims 10-21.

The present claims therefore have been split into the following unitary groups of inventions:
Invention 1: Claims 1-9: processes for the preparation of hydrated form of amorphous (S)-(+)-Clopidogrel bisulfate.
Invention 2: Claims 10-21: processes for the preparation of form I of (S)-(+)-Clopidogrel bisulfate.
Invention 3: Claim 22: process for the preparation of form II of (S)-(+)-Clopidogrel bisulfate.
Invention 4: Methods of treating cardiovascular and related diseases using (S)-(+)-Clopidogrel bisulfate; uses of (S)-(+)-Clopidogrel bisulfate for the preparation of a medicament for treating cardiovascular and related diseases.

The following examination has been performed for all inventions.

V. Reasoned statement

Reference is made to the following document:
D1: WO03/051362

Invention 1: Claims 1-9
Processes for the preparation of hydrated form of amorphous (S)-(+)-Clopidogrel bisulfate.

As explained in point III above, claims 1, 3 and 6 do not provide all technical features necessary to reliably and reproducibly obtain the desired product, without the use of inventive skill. They have therefore only been examined insofar as the antisolvent used in step ii. is one of those listed in claim 8.

Novelty

D1 discloses methods for preparing clopidogrel hydrogensulfate in amorphous form comprising the steps of preparing a solution of clopidogrel hydrogen sulfate in an alcohol selected from methanol and ethanol, removing the alcohol to obtain a residue, admixing an antisolvent with the residue to precipitate clopidogrel hydrogensulfate and separating the product (p. 6, l. 18-23). This general disclosure encompasses the present processes of claims 1-9. However, insofar as claims 1, 3 and 6 are concerned, these claims have only been considered in combination with claim 8, and D1 does not disclose any of the antisolvents listed in claim 8. Thus claims 1, 3 and 6 may be considered a novel selection insofar as the antisolvent used in these claimed processes is one of those of claim 8.

Although D1 discloses the use of conc. sulfuric acid to treat a solution of the free base in an alcohol to give the hydrogensulfate salt, there is no disclosure of using a solvent and water. Claims 2 and 5 may therefore be considered to be new.

Claims 1-9 fulfil the requirements of Article 33(2) PCT.

Inventive step

D1 describes the preparation of clopidogrel hydrogensulfate having at least one of the characteristics of amorphous form (see e.g. p. 6, l. 18-19). The technical problem underlying the present invention appears to be the provision of further methods for preparing such compounds.

For the processes of claims 1, 3 and 6 this problem has allegedly been solved by using as an antisolvent pentane, n-hexane, heptane, cyclohexane, pet ether or mixtures thereof. The most similar prior art processes, namely D1 examples 21, 27

and 44 result in a mixture of form I and amorphous form, form III and form VI, respectively. It would not be obvious from this document that the use of the above-mentioned antisolvents, rather than the MTBE used in D1, would reliably and reproducibly lead to the desired amorphous form. Therefore, insofar as the processes of claims 1, 3 and 6, using any "suitable solvent" in the sulfuric acid addition step and any "suitable antisolvent" from the list in claim 8, do indeed reliably and reproducible lead to the desired product, an inventive step may be recognised.

However, it is clear from D1 that small differences in reaction conditions and solvents lead to quite different products. The only "suitable solvent" exemplified in the present application for the processes of claims 1, 3 and 6 is methanol, and the only exemplified "suitable antisolvent" is cyclohexane. It may therefore be necessary in the regional phase of examination to provide further data demonstrating that the technical problem is indeed reliably and reproducibly solved over the entire scope of the claim, and not just the very restricted scope of the examples.

For the processes of claims 2, 4 and 5 the problem has allegedly been solved by treating the clopidogrel base in one or more suitable solvents and water with conc. sulfuric acid. The closest prior art processes, namely D1 examples 42 and 43, differ only in that the clopidogrel base in a suitable solvent (i.e. 2-butanol) in the absence of water is treated with conc. sulfuric acid. These processes lead to form V. It would not be obvious from the disclosure of D1 that by adding water to the "suitable solvent" the desired amorphous form would be obtained. Therefore, insofar as claims 2, 4 and 5 do indeed reliably and reproducibly lead to the desired product, an inventive step may be acknowledged for these claims.

In view of the fact that D1 teaches that small changes in reaction conditions may lead to different products, and the fact that the only "suitable solvent" exemplified in the present description is methanol, and the only exemplified "suitable antisolvent" is cyclohexane, it may be necessary in the regional phase of examination to provide further data demonstrating that the technical problem is indeed reliably and reproducibly solved over the entire scope of the claim, and not just the very restricted scope of the examples.

Claims 1-9 fulfil the requirements of Article 33(3) PCT.

Invention 2: claims 10-21
Processes for the preparation of form I of (S)-(+)-Clopidogrel bisulfate.

As explained in point III above, claims 10-15 do not provide all technical features necessary to reliably and reproducibly obtain the desired product, without the use of inventive skill. They have therefore only been examined insofar as the "suitable solvent" used is one of those listed in claim 20.

Novelty

No prior art has been found describing methods of preparing (S)-(+)-clopidogrel bisulfate using a C_{6-12} alcohol. Claims 10-15 and 20, insofar as they have been searched and examined, therefore appear to be new. Claim 21, insofar as it is dependent on claims 14 or 15, is also new for the same reasons.
Whilst D1 mentions both the treatment of clopidogrel base with H_2SO_4 and that a general method of accelerating crystallization is by seeding (p. 24, l. 1), no processes are disclosed in which both these features are present. Claims 16-19 and 21 (insofar as it is dependent on claims 18 or 19) appear to be new.

Claims 10-21 fulfil the requirements of Article 33(2) PCT.

Inventive step

The technical problem underlying claims 10-21 appears to be the provision of alternative methods for preparing (S)-(+)-clopidogrel bisulfate form I. D1 shows that different solvents and conditions lead to different products (amorphous form and/or forms I-VI). It would therefore not be obvious that by using one of the solvents listed in claim 20, the desired form I would be reliably and reproducibly obtained. Hence, insofar as the processes of claims 10-15 and 20 do indeed directly and inevitably lead to the desired product, an inventive step may be recognised for these claims. An inventive step may also be recognised on the same basis for claim 21, insofar as it is dependent on claims 14 or 15.

D1 mentions both the treatment of clopidogrel base with H_2SO_4 (p. 22, l. 21-28) and that a general method of accelerating crystallization is by seeding (p. 24, l. 1). Claims 16 and 17 concern processes involving the preparation of the bisulfate salt by treating the clopidogrel base with sulfuric acid, followed by seeding and separation of thus obtained form I crystals. Whilst different conditions may lead to different crystalline forms, it is well known that using seed crystals of a particular form will initiate or accelerate crystallisation of that particular polymorphic form from solution. It would be obvious for the skilled person to provide alternatives to the processes of D1 by adding seed crystals of form I to the solution of (S)-(+)-clopidogrel bisulfate. Claims 16 and 17 are not inventive. The way in which the clopidogrel base is formed does not appear to have any relevance to the polymorphic form of the bisulfate salt which crystallises out after seeding. Therefore the fact that the clopidogrel free base (which is subsequently converted into the bisulfate salt and crystallised by seeding) is prepared by basification of clopidogrel camphor-sulfonate merely appears to be an arbitrary choice from a number of ways to prepare the free base and cannot make the processes of claims 18, 19 and 21 (insofar as it is dependent on claims 18 or 19) inventive.

Claims 10-15 and 20 fulfil the requirements of Article 33(3) PCT.
Claims 16-19 and 21 do not fulfil the requirements of Article 33(3) PCT.

Invention 3: claim 22
Process for the preparation of form II of (S)-(+)-Clopidogrel bisulfate.

In view of the insufficiency of disclosure of this claim (see point III above) it was not possible to perform any meaningful examination of novelty or inventive step for this claim.

Invention 4: claims 23 and 24
Methods of treating cardiovascular and related diseases using (S)-(+)-Clopidogrel bisulfate; uses of (S)-(+)-Clopidogrel bisulfate for the preparation of a medicament for treating cardiovascular and related diseases.

Novelty

It is established practice at the European Patent Office that products are not rendered new simply because of the process by which they are produced, unless that process reliably leads to a product which is distinguishable from the prior art in some way [see PCT Guidelines 5.26 and A5.26[1]]. The presently described amorphous form, form I and form II do not appear to be distinguished from known forms of these compounds. Thus, claims 23 and 24 are directed to known uses of known forms of (S)-(+)-clopidogrel bisulfate (see e.g. D1, claim 81 directed to i.a. a method of inhibiting platelet aggregation comprising administering a pharmaceutical composition containing amorphous clopidogrel hydrogensulfate).

Claims 23 and 24 hence do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of their lack of novelty, claims 23 and 24 cannot be inventive.

Claims 23 and 24 do not fulfil the requirements of Article 33(3) PCT.

Inventions 1-4: claims 1-24

Industrial applicability

Claims 1-22 and 24 fulfil the requirements of Article 33(4) PCT.
No unified criteria exist in the PCT Contracting States for assessing whether present claim 23 is industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.